IN THE UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCE'S

In re application of:	Harry Meade
Serial No:	09/012,904
Filed:	January 1, 1998
For:	TRANSGENIC PRODUCTION OF ANTIBODIES IN MILK
Art Unit:	1636
Examiner:	Celine X. Qian
Attorney Docket Number:	GTC-1D3

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madame:

This application is before the Honorable Board of Appeals on appeal from the Final Rejection issued by the Examiner dated April 20, 2005 in connection with the above identified application, wherein all the claims under consideration, claims 19, 21, 25-27 and 29-35 were finally rejected. A Notice of Appeal was timely filed on October 19, 2005 and received and date stamped by the US Patent and Trademark Office on October 21, 2005.

Please charge the filing fee of $ 250.00 to GTC Biotherapeutics' Deposit Account No. 502092, in compliance with 37 CFR § 1.17(c). As required by 37 CFR § 1.192 this Brief is filed in triplicate. The petition for an extension of time is also attached, please charge the fee of $1080.00 for a five-month extension of time for a small entity and any deficiencies to the GTC Biotherapeutics' Deposit Account No. 502092. Accordingly, this brief is timely filed.

CERTIFICATE OF MAILING BY EXPRESS MAIL

I hereby certify that under 37 CFR §1.10 that this correspondence is being deposited on May 18, 2006 with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

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Dawn Greenaway

REQUEST FOR ORAL HEARING

An oral hearing is requested. Please charge the fee of $500.00 and any deficiencies to the Applicants' Deposit Account No. 502092.

(1) REAL PARTY IN INTEREST

GTC Biotherapeutics, Inc.
175 Crossing Blvd., Suite 410
Framingham, MA 01702

This application has been assigned to Genzyme Corporation (whose successor in interest is GTC Biotherapeutics, Inc.) by the Inventors. A copy of the Assignment signed by the Inventors of the instant application to Genzyme Corporation was recorded with the US Patent and Trademark Office on March 22, 1994 and can be found at Reel 6931, Frame 0712. Genzyme Corporation thereafter assigned the instant application to Genzyme Transgenics Corporation. A copy of the Assignment from Genzyme Corporation to Genzyme Transgenics Corporation was recorded on March 31, 2005 and can be found at Reel 7406, Frame 0113. A Change of Name document was recorded with the US Patent and Trademark Office on June 27, 2003 and can be found at Reel 013782, Frame 0450 changing the name of Assignee from Genzyme Transgenics Corporation to GTC Biotherapeutics, Inc. A corrective to the Change of Name was filed thereafter and recorded on October 20, 2003 and can be found at Reel 014162, Frame 0255. As such, real party interest lies with GTC Biotherapeutics, Inc.

(2) RELATED APPEALS AND INTERFERENCE'S

To the best of Applicant's knowledge there are no appeals or interference actions that will be affected by this appeal.

(3) STATUS OF CLAIMS

Claims 19, 21, 25-27 and 29-35 are pending in the application. Claims 19, 21, 25, 29 and 30 remain in this case and were last amended by an Amendment dated February 8, 2005.

(4) STATUS OF AMENDMENTS

The Examiner entered the amendments made in the Applicant's response dated February 8, 2005. No amendments have been filed subsequent to the Examiner's entrance of the Final Rejection on April 20, 2005.

(5) SUMMARY OF THE INVENTION

Claims 19, 21, 25-27 and 29-35 are directed to the production of recombinant immunoglobulin molecules in the milk of transgenic non-human mammals. That is, the expression system of the current claims focuses on transgenic mammals and was developed to overcome not only the problems that transgenic animals have with the expression of fusion proteins generally, but also the problems associated with the production and assembly of biologically active immunoglobulins specifically.

Applicants point out that the claims are directed to DNA constructs for providing a heterologous immunoglobulin in the milk of a non-human transgenic mammal. These constructs also include as a necessity for expression a promoter sequence that results in the preferential expression of a protein-coding sequence in mammary gland epithelial cells, an immunoglobulin protein-coding sequence, a 3' non-coding sequence; and a unique restriction site between the promoter and the 3' non-coding sequence, wherein the immunoglobulin protein-coding sequence is inserted into the restriction site.

Applicants realized that by using recombinant DNA technology it was possible to program cells other B-lymphocytes to express immunoglobulin genes. Moreover, they realized that non-human mammals could be engineered to produce recombinant human antibodies that were biologically active and assembled properly. The difficulties

encountered in this effort stemmed from several factors: 1) both heavy and light chains of the desired immunoglobulin must be co-expressed at appropriate levels; 2) nascent immunoglobulin polypeptides undergo a variety of co- and post-translational modifications that may not occur with sufficient fidelity or efficiency in in vitro cell cultures; 3) immunoglobulins require accessory proteins for their assembly; 4) the synthetic and expression capacity of in vitro cell cultures may be inadequate for the large amount of antibody needed commercially; and 5) the expressed recombinant immunoglobulins may be unstable in the extracellular milieu of a foreign cell.

The current invention provides, in overcoming the difficulties provided above, provided techniques for obtaining heteroloqous immunoglobulins from the milk of transgenic mammals. In so doing it comprises methods for the creation of transgenic non-human mammals by introducing into their germline immunoglobulin cDNA linked to a milk-specific promoter

Independent claim 19 provides for the production of target immunoglobulin molecules for secretion in milk.

Case Law Made of Record, or Relied Upon by the Examiner

a) In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)

b) In re Jones, 958 F.2d 347 (Fed. Cir. 1992)

References Relied Upon or Made of Record during Prosecution of this Case by the Examiner

a) Bischoff et al., FEBS LETTERS 305:265-68 (1992)

b) Buhler et al., BIO/TECHNOLOGY 9:835-38 (1991)

c) DeBoer et al., United States Patent No.# 5,633,076 for, "METHOD OF PRODUCING A TRANSGENIC BOVINE OR TRANSGENIC BOVINE EMBRYO."

d) Ebert et al., BIO/TECHNOLOGY 8:140-43 (1990)

e) Gordon et al., BIO/TECHNOLOGY 5:1183-87 (1987)

f) Meade et al., United States Patent No.# 4,873,316 for, "ISOLATION OF EXOGENOUS RECOMBINANT PROTEINS FROM THE MILK OF TRANSGENIC MAMMALS."

g) Stinnakre et al., FEBS LETTERS 284:19-22 (1991)

References Made of Record or Documents Relied Upon by the Applicants

a) Bischoff et al., FEBS LETTERS 305:265-68 (1992)

b) Buhler et al., BIO/TECHNOLOGY 9:835-38 (1991)

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f) Meade et al., United States Patent No.# 4,873,316 for, "ISOLATION OF EXOGENOUS RECOMBINANT PROTEINS FROM THE MILK OF TRANSGENIC MAMMALS."

g) Stinnakre et al., FEBS LETTERS 284:19-22 (1991)

h) Manual of Patent Examination and Procedure (8^{th} ed.) §§ 2141; 2173.02.

i) R. Harmon, **PATENTS AND THE FEDERAL CIRCUIT** § 4.7 (3d edit. 1994).

Case Law Made of Record, or Relied Upon by Applicants

a) Ajinomoto Co., Inc. v. Hering-Daniels-Midland Co., 228 F.3d 1338, 1340 (Fed. Cir. 2000).

b) Ashland Oil Inc., v. Delta Resins & Refractories, Inc., 776 F.2d 281 (Fed. Cir. 1985).

c) In re Bell, 991 F.2d. 781, 26 U.S.P.Q. 1529 (Fed. Cir. 1993).

d) In re Borkowski, 422 F.2d 904, 164 USPQ 214 (CCPA 1970).

e) Carella v. Starlight Archery, 231 U.S.P.Q. 644 (Fed. Cir. 1986).

f) In re Collier, 397 F.2d 1003, (CCPA 1968).

g) In re Dillon, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990)(*en banc*).

h) Enzo Biochem v. Calgene, Inc., 188 F.3d 1362 (Fed. Cir.1999).

i) Enzo Biochem v. Gen-Probe, Inc., 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002).

j) In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

k) In re Geiger, 815 F.2d 686, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987).

l) Graham v. John Deere Company, 383 U.S. 1, (1966).

m) Lindemann Maschinefabrik GMBH v. American Hoist and Derrick Co., 221 U.S.P.Q. 481 (Fed. Cir. 1984).

n) In re Moore, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971).

o) In re Myers, 410 F.2d 420, 161 USPQ 668 (CCPA 1969).

p) Northern Telecom Inc., v. Datapoint Corp., 121 F.2d 931, 934 (Fed. Cir. 1990).

q) In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

r) Pro-Mold & Tool Co., Inc. v. Great Lake Plastics, Inc., 75 F.3d 1568, at 1573 (Fed. Cir. 1996).

s) In re Rijckaert, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993).

t) In re Thorpe, 777 F.2d 695, 697, 227 USPQ 964, 966 (Fed. Cir. 1985).

u) In re Vaeck, 947 F.2d 488, at 496 (Fed. Cir. 1991).

v) In re Venezia, 530 F.2d 956, (CCPA 1976).

w) Webster Loom Co. v. Higgins, 105 U.S. 580, 26 L.eD. 1177, 1179 (1882).

x) In re Wiggins, 179 USPQ 421 (CCPA 1973).

(6) ISSUE

The Board must decide:

I. Are claims 19, 21, 25-27, 29 and 30 allowable under 35 U.S.C. §112, first paragraph?

II. Are claims 19, 21, 25-27, 29 and 30 allowable under 35 U.S.C. §112, second?

III. Are claims 19, 25-27 allowable under 35 U.S.C. §103(a) over Meade et al., (U.S. patent No. 4,873,316), in view of DeBoer *et al.*, (U.S. Patent No. 5,633,076)?

IV. Is claim 21 allowable under 35 U.S.C. §103(a) over Meade et al., (U.S. patent No. 4,873,316), in view of DeBoer *et al.*, (U.S. Patent No. 5,633,076) when taken in light of Buhler et al., Bishoff et al., Gordon et al., Ebert et al., and Stinnakre et al?

(7) GROUPING OF CLAIMS

For purposes of this appeal, the Claims 19, 21, 25-27 and 29-35 are not argued separately, and stand or fall together.

(8) ARGUMENT

I. With Respect to Issue I

Claims 19, 21, 25-27, 29 and 30 stand rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. With regard to the disclosure presented in the current application, the 'enablement' rejections provided

here for lack of fulfilling the written requirement are answered not only by the series of amendments to the claims to more particularly point out the novelty of the current invention but also by reference to the MPEP for guidance on how much guidance is necessary to provide to an average artisan in the field of the invention.

Experimentation

At the outset it must stated that the specification, to the limited extent it is necessary in the instant case, is not required to teach every detail of the invention or to perform the function of a technical production manual/specification. The specification need only explain how to make and use the invention without requiring an inordinate amount of experimentation. Moreover, even the possibility that experimentation needed may be complex does not necessarily make it undue if a person skilled in the art typically engages in such experimentation. In re Borkowski, 422 F.2d 904, 164 USPQ 214 (CCPA 1970). In fact, enablement itself is a legal issue (citations omitted), and the issue is resolved by asking the question whether or not the instant disclosure is, coupled with the prior art sufficient to enable those skilled in the art to practice the claimed invention. In this way a specification need only present those elements of the invention which are novel, avoiding the need to supply a vast treatise on a given area of technology every time an application is filed. The prior art therefore is available and expected to fill any gaps that the instant specification might have with regard to enablement. In re Myers, 410 F.2d 420, 161 USPQ 668 (CCPA 1969). Lindemann Maschinefabrik GMBH v. American Hoist and Derrick Co., 221 U.S.P.Q. 481 (Fed. Cir. 1984); Ajinomoto Co., Inc. v. Hering-Daniels-Midland Co., 228 F.3d 1338, 1340 (Fed. Cir. 2000)("Patents, however, are written to enable those skilled in the art to practice the invention, not the public"); Enzo Biochem v. Calgene, Inc., 188 F.3d 1362 (Fed. Cir.1999); *and see*, Enzo Biochem v. Gen-Probe, Inc., 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002).

The working examples provided in the specification, and the functional knowledge of basic antibody molecules and the requirements needed for their expression in a recombinant form provide the assurance that any needed experimentation will not be "undue" and will amount to little more than routine optimization.

In a broad sense the novelty of the patent lies, as expected, in the novel manipulation and engineering of immunoglobulin molecules, their physiological activity and overcoming the limitations of the prior art. The fact that the prior art did not contemplate the generation and use of the recombinant antibodies of the invention, while the Applicants provide and claim a working example and a written protocol of such is the precise reason why the current application is patentable -- it is novel.

The extensive uses of the antibodies disclosed in the specification, knowledge of their nucleic acid sequences and the Applicants knowledge of transgenic mammal generation combined to create and reduce to practice the instant invention. That is, by providing a detailed map leading towards a goal that has already been reached, regardless of the state of the art prior to the application. In conjunction with the extremely high level of skill in the field, it is clear that the specification, as tempered by the relevant case law discussed above, does provide "adequate" guidance to make and use the invention. In re Vaeck, 947 F.2d 488, at 496 (Fed. Cir. 1991).

Indeed, the application presents the essential features of the molecular manipulations necessary to carry out the invention. Moreover, the Applicants eliminate the need for any undue experimentation by providing examples in the specification. This level of disclosure is **more than** what is necessary for a specification to provide. In determining whether the disclosure requirement is satisfied, the person(s) *skilled* in the art are *presumed* to be aware of all of the relevant literature, including trade publications, textbooks, technical journals, and U.S. patents. Whereupon, the disclosure of a relevant discovery and subsequent allowance as a patent, would then provide a variety of potential uses for those skilled in the art, as mentioned above. With regard to the nature of the specification in the instant matter, the uses therein disclosed need not be apparent to everyone, all that is required is that enablement, and the potential usefulness of the discovery is communicated to the skilled artisans of the relevant technology.

Respectfully the Applicants maintain that this communication was sufficiently performed in the specification. Therefore, the Examiners rejection of the claims under 35

U.S.C. § 112, first paragraph, is respectfully traversed. Webster Loom Co. v. Higgins, 105 U.S. 580, 26 L.eD. 1177, 1179 (1882).

II. With Respect to Issue II

Claims 19, 21, 25-27, 29 and 30 are rejected under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The essential question under 35 U.S.C. 112, second paragraph, is whether the claims do, in fact, set out and circumscribe a particular area with a reasonable degree of precision and particularity. Here the Examiner has stated that the recitation of both a heavy and a light chain clause causes the rejected claims to essentially be 'vague' and fail to convey the invention provided by the Applicants. Respectfully, the sole remaining independent claim recites an "immunoglobulin" or antibody. Within the context of the Specification and the ability of the Inventor to be his own lexicographer this means a physiologically active antibody that is properly 'assembled.' In order for this to be true the transgenically produced antibody will, as is well known by science, require the assembly of both heavy and a light chains in equivalent numbers to form a 'normal' antibody structure. This works with the knowledge implicit to workers in the field that both heavy and light chains are needed in stoichiometric amount for proper assembly. Thus the claims as amended are definite, lay out precisely the metes and bounds of the invention, and provide needed essential elements. See, In re Venezia, 530 F.2d 956, (CCPA 1976); In re Collier, 397 F.2d 1003, (CCPA 1968). It is important to point out that the definiteness of claim language is analyzed, not in a vacuum, but always in light of the Specification and the teachings of the prior art as they would be interpreted by one possessing the ordinary level of skill in the pertinent art. In re Moore, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). See also MPEP § 2173.02. Therefore it is the Applicants contention that the scope of the invention is clearly laid out from the language of the claims, and that therefore a 35 U.S.C. 112, second paragraph rejection is inappropriate. In re Wiggins, 179 USPQ 421 (CCPA 1973).

III. With Respect to Issue III

Claims 1, 4-7, 10-13 and 16-18 were rejected under 35 U.S.C. §103(a) as being obvious in light of Meade et al., and DeBoer et al. As seen below this rejection is, respectfully, improper and should be reversed.

ARGUMENT

Establishment of a *prima facie* case of obviousness is a procedural tool for allocating the burden of proof as between an Applicant and the Examiner. The initial burden is upon the Examiner to present this *prima facie* case of obviousness to negative patentability. Without such an affirmative showing Applicant is entitled to a patent grant. Respectfully, in the current case the Examiner has failed to establish the needed case of obviousness, without more, entitling the Applicant to a patent grant. In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

Regarding the required establishment of *prima facie* obviousness, the Applicant points out why the cited prior art of Meade et al., and DeBoer et al. are simply not up to this task. The appropriate test for obviousness was enunciated by the United States Supreme Court's in Graham v. John Deere Company, 383 U.S. 1, 17, 148 U.S.P.Q. 459, 467 (1966). More to the point, analysis of the instant claims leads to the conclusion that these claims are not obvious over the cited prior art reference. *Graham* sets forth, the factual inquiries necessary to determine obviousness. These are as follows:

1. The scope and content of the prior art are to be determined;
2. The differences between the prior art and the claims at issue are to be ascertained; and

3. The level of ordinary skill in the pertinent art is to be resolved.

Graham directs that it is against this background that the obviousness issue is determined.

Establishment of a *prima facie* case of obviousness is a procedural tool for allocating the burden of proof as between an Applicant and the Examiner. The initial burden is upon the Examiner to present this *prima facie* case of obviousness to negative patentability. Respectfully, in the instant case previously reviewed by the Examiner no such case of obviousness has been established. Thus, without more the Applicant is entitled to a grant of the patent. In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

A. Prima Facia Obviousness

A *prima facie* case of obviousness is established when the teachings from the prior art itself suggest the claimed subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d. 781, 26 U.S.P.Q. 1529 (Fed. Cir. 1993); In re Rijckaert, 28 U.S.P.Q.2d 1955 (Fed. Cir. 1993). The basic considerations which apply to obviousness rejections under MPEP § 2141 are as follows:

1. the claimed invention must be considered as a whole;
2. the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
3. the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and
4. reasonable expectation of success is the standard by which obviousness is determined.

When the prior art itself fails to meet even one of the above criteria the cited art does not satisfy 35 U.S.C. § 103(a) and prevents the establishment of the required *prima facie* case of obviousness by the Examiner. In re Oetiker, 977

F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992); In re Rijckaert, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). As pointed out above, the Meade reference not only fails to render obvious the current claims it also fails to provide any incentive to combine with other prior art.

It is also important to point out that there is no requirement in patent law that the a patentable product be produced by non-obvious or novel methods, regardless of whether that product is a DNA construct, or an amino acid sequence but only that the product itself be non-obvious. In re Bell, 26 USPQ2d 1529 (Fed. Cir. 1993); In re Thorpe, 777 F.2d 695, 697, 227 USPQ 964, 966 (Fed. Cir. 1985). As an example, the Federal Circuit upheld this principle in Bell where the court found that the genes for human insulin like growth factors I and II (IGF) were not rendered obvious by the previously disclosed full amino acid sequences, thus providing an even narrower patentability for a difference even narrower than that enunciated by the Examiner here.

In determining obviousness, the basic issue is whether applied references, alone or in any combination, suggest the claimed invention as a solution to the specific problem solved. When the prior art itself does not suggest or render obvious the claimed solution to that problem, the art involved simply does not satisfy the criteria of 35 U.S.C. § 103 for precluding patentability. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion, or incentive supporting the combination. Carela v. Starlight Archery, 231 U.S.P.Q. 644 (Fed. Cir. 1986).

The critical inquiry in combining various prior art references is whether there is some reason or motivation to combine present in the prior art as a whole that would motivate a person of ordinary skill in the art to combine those references. Pro-Mold & Tool Co., Inc. v. Great Lake Plastics, Inc., 75 F.3d 1568, at 1573 (Fed. Cir. 1996). When the party challenging patentability relies upon a combination of prior art to so establish, then that party then bears the burden of showing some teaching or suggestion in the references for the combination. Ashland Oil Inc., v. Delta Resins & Refractories, Inc., 776 F.2d 281 (Fed. Cir. 1985). As a Federal Circuit court stated over a decade ago:

> "It is insufficient that the prior art disclosed the components of the patented device, either separately or used in other combinations; there must be some teaching, suggestion, or incentive the make the combination made by the inventor." Northern Telecom Inc., v. Datapoint Corp., 121 F.2d 931, 934 (Fed. Cir. 1990). In this sense it is improper to the Applicant's ideas as a instruction manual on reconstituting the prior art. R. Harmon, **PATENTS AND THE FEDERAL CIRCUIT** § 4.7 (3d edit. 1994).

No such suggestions were, respectfully, made in the cited prior art and therefore the case for obviousness can be made.

B. Citations

Meade et al.,

As previously stated, the Meade et al, patent provides some insight and teachings in the use of DNA constructs and in the development of transgenic animals for the production of biopharmaceuticals in milk. However, the teachings of Meade et al., do not by themselves or in combination with any of the other cited art render the instant claims obvious.

The subject matter of the remaining claims is directed to DNA constructs for providing a heterologous immunoglobulin in the milk of a non-human transgenic mammal. The construct of the invention includes an appropriate promoter sequence that results in the preferential expression of a protein-coding sequence in mammary gland epithelial cells, an immunoglobulin protein-coding sequence, a 3' non-coding sequence; and a unique restriction site between the promoter and the 3' non-coding sequence, wherein the immunoglobulin protein-coding sequence of interest is inserted into the restriction site.

More to the point for the immediate claims is objective fact that Meade et al., patent fails to provide or teach the following:

I. Meade et al. fails to teach or suggest that expressing the light chain and heavy chain of an immunoglobulin separately by using a mammary epithelial cell comprising at least two vectors, one encoding the heavy chain and one encoding the light chain. Meade et al., simply fails to contemplate expressing these chains

separately;

II. Meade et al., fails to teach a separate construct for the light chain and the heavy chain for the production of a single immunoglobulin species;

III. Meade et al, fails to indicate that the use of two separate vectors can result in a cell capable of producing an assembled, functional immunoglobulin in milk;

IV. Meade et al., fails to disclose a unique restriction between the promoter and the 3' non-coding sequence, wherein the immunoglobulin coding sequence is inserted into the restriction site;

V. Meade et al. fails to teach that the claimed construct should have a unique restriction site in between the promoter and the 3' untranslated region into which an immunoglobulin protein-encoding sequence is inserted; and,

VI. Meade et al., fails to teach the unique construction of the restriction site – such that it has a coding sequence inserted into the site- that then allows for a vector which can easily be modified, without the need for cleaving the remaining construct to insert various immunoglobulin chains is an improvement over the prior art. This construction allows for easier expression of a variety of different immunoglobulin coding sequences. Thus, the use a unique restriction site into which the immunoglobulin coding sequence is inserted, adapts to the unique features of expressing immunoglobulins.

As can be seen from the amended claims, each of the above elements provided are integrated into the pending claims. Given this, and the controlling precedent cited above, the cited prior art simply fails to render the instant invention obvious. Reconsideration of the rejected claims is respectfully requested.

DeBoer et al,

DeBoer et al., does not provide what Meade lacks, see "I" through "VI" above. Importantly, neither Meade et al. nor DeBoer et al. teach or suggest the claimed construct having a unique restriction site in between the promoter and the 3' untranslated region into which an immunoglobulin protein-encoding sequence is inserted. DeBoer also fails with regard to each and every other element called out above as deficient in Meade et al. Respectfully, the lack of even one element I – VI as provided above is sufficient to prevent an obviousness rejection from being maintained.

Respectfully, and to clarify the Applicants position DeBoer et al. does not make up for any of the other deficiencies of the Meade et al. reference. Specifically, the Applicants understand the assertion of the Examiner that DeBoer et al., at Column 30 lines 45-50 and Figure 7E provides for the development of a construct having a casein promoter and a 3' non-coding sequence, and unique restriction sites, including XhoI, between the promoter and the 3' coding sequence. Applicants again state , however, that neither the textual citation of DeBoer or the Figure relied upon by the Examiner demonstrates a mammary gland specific promoter and a 3' non-coding region wherein there is a unique restriction site into which an immunoglobulin-coding sequence has been inserted. Therefore, this citation simply does not present the elements of the current invention regarding the production fully-functional, fully-assembled immunoglobulins in transgenic mammalian milk. It does not attempt to teach this modification of the prior art. Moreover, it does not teach any combination with Meade et al.

Thus, amended independent claim 19, which recites elements not rendered obvious by Meade or DeBoer alone or in combination, cannot be obvious as against either of these references. Therefore, the Examiner's rejections are traversed and reconsideration is respectfully requested. Reconsideration is respectfully requested.

Dependent claims 25-27 and 30 being dependent upon and further limiting independent amended claim 19 should also be allowable for those reasons, as well as for the additional recitations they contain. Applicants respectfully request reconsideration of the rejection of claims 19, and 25-28 under 35 U.S.C. § 103(a) in view of the above amendments and remarks.

Respectfully, it is thus the objective measure of obviousness that the prior art cited of record is incapable of supporting, thus preventing the maintenance of a 35 U.S.C. §103(a) rejection. Applicants therefore overcome the rejection of the amended claims under 35 U.S.C. §103(a) as being unpatentable over Meade et al., in view of DeBoer et al.

IV. With Respect to Issue IV.

Buhler et al., Bishoff et al., Gordon et al., Ebert et al., and Stinnakre et al.,

Claim 21 stands rejected under 35 U.S.C. §103(a) as being unpatentable over the Meade et al., DeBoer et al., references when taken in view of Buhler et al., Bishoff et al., Gordon et al., Ebert et al., and Stinnakre et al.,

As stated during prosecution, the citations cited immediately above do not teach or suggest the claimed invention. Rather Bischoff et al., Buhler et al., Gordon et al., Ebert et al, and Stinnakre et al. are merely relied upon by the Examiner for their disclosure of specific milk protein promoters, namely whey acid promoter and lactalbumin promoter and none of these references make up for the deficiencies of Meade et al. and DeBoer et al., outlined above. Therefore, Applicants respectfully suggest that this ground of rejection is overcome.

Respectfully, the Examiner must provide more than an odd collection of references that recast pieces of known technology, and other elements that may hint at the novelty created by the Applicants in the instant invention. The Examiner must provide references that ***knowingly*** suggest the combination of protocols, tests, or principles, which will lead to the invention to be rendered obvious, and read upon its claims. The Examiner has not provided these references. Rather the Examiner has stated that the instant claims are obvious "to one of ordinary skill" (Office Action of December 17, 2002, page 6, last paragraph). Without more, this is a classic reproduction of the invention from improper hindsight, which cannot be used to negative

patentability or establish the required case of *prima facie* obviousness. In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

The important point here is that with regard to the above rejections under 35 U.S.C. §103(a), it should be pointed out that to support the combination of various sources to create an obviousness rejection those sources must themselves specifically contain or objectively suggest to the skilled artisan a combination of art to achieve the invention. To allow anything less would be to render 35 U.S.C. §103(a) a subjective measure of patentability without any parameters or objective standards. This is what the Federal Circuit has squarely decided against in its statements about the improper application of hindsight to sustain an obviousness rejection. This is why the disclosures drawn upon by an Examiner must explicitly contain all the necessary techniques and suggest the combination that would lead to the invention as claimed in a factual and objective way. In re Dillon, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990)(*en banc*); In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Geiger, 815 F.2d 686, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). This the multitude of references cited by the Examiner does not do. Respectfully, the shear number of references cobbled together does much to underscore the novelty of the instant claims.

It should be noted that in response to the Examiner's very thorough comments that existing independent claim 19 has been extensively amended herein to address a variety of the Examiner's concerns as well as to ameliorate some structural and grammatical problems with the claims. Therefore Applicant requests reconsideration of claim 21 in light of these amendments and claim additions. Given the analysis above, the Examiner's remaining objections to the claims as amended are respectfully traversed. Respectfully, it is thus the objective measure of obviousness that the prior art cited of record is incapable of supporting, thus preventing the maintenance of a 35 U.S.C. §103(a) rejection. Applicants therefore respectfully request the withdrawal of the Rejection of claims 21 under 35 U.S.C. §103(a). Reconsideration is respectfully requested.

V. CONCLUSION

In light of the above remarks and the limits of the outstanding claims Applicant respectfully submits that the Examiner fails to maintain the required case of *prima facie*

obviousness under 35 U.S.C. § 103(a) in this case and that the rejections based on failure to adequately provide for the requirement of 35 U.S.C § 112, first & second paragraphs are traversed. Therefore, Applicant respectfully notes that final impact of these failures must be the reversal of the Final Rejection issued by the Examiner and allowing the claims.

Therefore, based upon the arguments made herein, Applicant requests that the Examiner's rejections of the pending claims be reversed, and those said claims be allowed to go to issue.

Respectfully submitted,

Date: 5/17/06

By: _____

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APPENDIX
BOARD OF PATENT APPEALS AND INTERFERENCE'S
APPEAL BRIEF

In re application of:	Harry Meade
Serial No:	09/012,904
Filed:	January 1, 1998
For:	TRANSGENIC PRODUCTION OF ANTIBODIES IN MILK
Art Unit:	1636
Examiner:	Celine X. Qian
Attorney Docket Number:	GTC-1D3

THE CLAIMS ON APPEAL

1-18 (Cancelled)

19. (Previously Presented) A DNA construct for providing a heterologous immunoglobulin in the milk of a non-human transgenic mammal comprising a promoter sequence that results in the preferential expression of a protein-coding sequence in mammary gland epithelial cells, an immunoglobulin protein-coding sequence, a 3' non-coding sequence; and a unique restriction site between the promoter and the 3' non-coding sequence, wherein the immunoglobulin protein-coding sequence is inserted into the restriction site; and wherein said DNA construct is integrated into the genome of said mammal in such a way that said protein-coding sequence is expressed in the mammary gland of said mammal, and secreted from said mammary gland in the milk of said mammal; and,

wherein the expressed immunoglobulin protein sequence is primarily or completely of human origin, wherein each coding region may be expressed individually and,

wherein the immunoglobulin protein-coding sequence encodes a heavy chain coding region;

wherein said immunoglobulin protein-coding sequence encodes a light chain coding region.

20. (Cancelled)

21. (Previously Presented) The construct of claim 19 wherein said promoter is selected from the group consisting of a beta lactoglobulin promoter, a whey acid protein promoter, and the lactalbumin promoter.

22-24. (Cancelled)

25. (Previously Presented) The construct of claim 19 wherein said promoter is a casein promoter.

26. (Previously Presented) The construct of claim 19, wherein the restriction site is an XhoI restriction site.

27. (Previously Presented) The construct of claim 19, wherein the 3' non-coding sequence is a 3' non-coding region from a mammary-specific gene.

28. (Cancelled)

29. (Previously Presented) A mammary gland epithelial cell comprising the construct of claim 19 and a construct comprising an immunoglobulin protein-coding sequence which encodes both a light chain and a heavy chain, operatively linked to a promoter sequence that results in the preferential expression of the protein-coding sequence in mammary gland epithelial cells, wherein the cell expresses the light and heavy chains separately and secretes a heterologous, assembled immunoglobulin comprising the light and heavy chains.

30. (Previously Amended) A mammary gland epithelial cell comprising the construct

of claim 19 further comprising wherein the cell expresses the light and heavy chains separately and the sequences so expressed are fully human sequences; and,

wherein said promoter sequence is selected from a group consisting of: beta lactoglobulin promoter, casein promoter, whey acid protein promoter, and the lactalbumin promoter.

31-35 (Withdrawn)